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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,943	03/02/2004	William R. Wilson	8654/2222	2176

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/790,943	WILSON ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,8,11-13,16,17,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8,11-13,16,17,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 1-4, 7-8, 11-13, 16-17 & 20-21 ARE PRESENTED FOR EXAMINATION

Applicants' amendment filed 4/16/2007 has been received and entered into the application. Accordingly, claims 1-4, 7-8, 11, 13, 16-17 and 20-21 have been amended.

In view of the above amendments, the objection of claims 3, 4, 8, 13 and 17 and the rejection of claims 1-4, 7-8, 11-13, 16-17 and 20-21 under 35 U.S.C. 112, 1st Paragraph (Written Description) have been overcome and are hereby *withdrawn*. The following rejections are either reiterated or newly applied and constitute the totality of issues remaining in the present application.

Priority

For clarification, the Examiner has not denied Applicants' claim of foreign priority to GB0121285.1. The Examiner, in the previous Office Action, was simply noting that a certified copy had not been filed in the instant case and was not implying that there was a requirement that Applicants do so.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were

made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1-4, 7-8, 11-13, 16-17 and 20-21 are again rejected under 35 U.S.C. § 103(a) as being unpatentable over Siemann *et al.* (Proceedings of the American Association for Cancer Research, 2000, vol. 41, page 525) in view of Pruijn *et al.* (Cancer Chemother. Pharmacol., 1997, col. 39, pages 541-546) and van Moorsel *et al.* (Biochemical Pharmacology, 1999, vol. 57, pages 407-415) (all prior art of record).

Applicants' arguments (see Response filed 4/16/2007) have been fully considered but they fail to persuade the Examiner of an error in his determination of obviousness.

Firstly, Applicants argue that there can be no basis to obtain the combination instantly claimed based on Siemann, Pruijn or van Moorsel, alone or in combination. Applicants base this argument on the fact that no single reference discloses gemcitabine in combination with DMXAA. However, the Examiner notes that the present rejection is an *obviousness* rejection, not an anticipation rejection. As such, the question is whether the subject matter, as a whole, would have been obvious to one of ordinary skill in the art at the time of the invention, not whether any given reference teaches all the limitations of the instant claims.

Secondly, Applicants argue that the drugs combined with DMXAA in the prior art are crosslinking agents, whereas gemcitabine is not. This argument is not persuasive because the mechanism of action of the drugs is not at question here. As discussed in the

previous Office Action, it is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose (*In re Kerkoven*, 205 U.S.P.Q. 1069 (CCPA 1980)). With respect to *Kerkoven*, Applicants assert that this case law is unrelated to the present fact pattern, going so far as to call Examiner's citation of *Kerkoven* "an excercise in *reductio ad absurdum*" (page 8 of Response). Examiner respectfully points out to Applicants that *Kerkoven* is not relied upon to provide the motivation to combine in the instant case. Such motivation comes explicitly from the cited references. However, even if there were no motivation found in the cited references, the prior art is replete with examples of chemotherapeutic drugs being combined to treat cancer. As such, it is not seen as inventive to combine DMXAA and gemcitabine, both of which were known in the art as anticancer treatments and both of which have been combined with other anticancer agents.

Thirdly, with respect to Applicants' request that the Examiner explain the basis of his "natural presumption" that two known anticancer drugs, when combined, provide a third composition useful to treat cancer, the Examiner respectfully requests that the Applicants provide more than the single cited article to rebut this natural presumption. As noted *supra*, the prior art is replete with examples of two anticancer agents being safely combined to form a third composition to treat cancer (see, for example, the references used in the present rejection). The natural presumption is that such a combination will be effective and safe. Applicants' citation of a single combination (capecitabine and docetaxel) that causes hand-foot syndrome is not sufficient to rebut Examiner's presumption, which is based on the overwhelming amount of literature

readily available in the prior art that demonstrates the effectiveness of anticancer drug combinations.

Finally, with regard to synergy, Applicants argue that not all chemotherapeutics show synergy when used in combination with DMXAA. For example, Applicants point to Table 1 of the application where it is shown that **one** (5-fluorouracil) out of seven (14%) drugs tested did not show synergism when combined with DMXAA. The Examiner respectfully suggests that Table 1 supports his position that the skilled artisan would **reasonably expect** to see synergism when a given anticancer drug is combined with DMXAA. In fact, 86% of the drugs tested by Applicants showed synergism when combined with DMXAA. Another drug not tested by Applicants (melphalan) has also shown synergism when combined with DMXAA (Pruijn *et al.*). In addition, there are three *expected* effects that may arise from combination therapy: 1) an additive effect; 2) a synergistic effect; and 3) antagonism. For example, if Compound A and Compound B each increase life expectancy by 1 month when administered as single agents, the skilled artisan would expect that a combination of Compound A and Compound B would: 1) increase life expectancy by 2 months (additive); 2) increase life expectancy by *more* than 2 months (synergistic); or 3) decrease life expectancy (*less* than 1 month) (antagonism). The fact that Applicants have shown that a combination of DMXAA and gemcitabine is synergistic only demonstrates one of three expected results. Similarly, if Applicants had shown an additive effect, this too would have been expected. By asserting that a synergistic result is "unexpected", Applicants are implying that only an additive or antagonist effect would be expected. This is simply not the case, especially in a

combination of DMXAA and other anticancer drugs, which have been shown in the prior art to be synergistic.

Accordingly, the claims are deemed properly rejected under 35 U.S.C. § 103 as being obvious over Siemann *et al.* in view of Pruijn *et al.* and van Moorsel *et al.* The rejection of claims 1-4, 7-8, 11-13, 16-17 and 20-21 is maintained for the reasons of record and reiterated below.

The instant claims are drawn to methods, compositions, and kits comprising DMXAA and gemcitabine. Dependent claims recite that the agents are in a potentiating ratio.

Siemann *et al.* disclose that DMXAA enhances (*i.e.* potentiates) the efficacy of the chemotherapeutic agents cisplatin and cyclophosphamide in rodent (KHT sarcoma) and human (SKBR3 breast and OW1 ovarian carcinoma) tumor models. DMXAA (17.5 mg/kg) was shown to increase the tumor cell kill of cisplatin and cyclophosphamide by 10-500 fold over that seen with chemotherapy alone (Abstract). The reference thus demonstrates that DMXAA potentiates the antitumor effect of two traditional chemotherapeutic agents in a mammalian tumor model of breast and ovarian tumors. The reference does not disclose combining DMXAA with gemcitabine.

Pruijn *et al.* also disclose enhancing the antitumor activity of an anticancer agent, in this case melphalan, by co-administering melphalan with DMXAA (Abstract). DMXAA is well known in the art as an antitumor agent that inhibits tumor blood flow (page 541, right column, "Introduction"). DMXAA is also disclosed to enhance the antitumor effects of hypoxia-selective cytotoxins (*id.*). DMXAA was formulated in phosphate-buffered saline and melphalan was dissolved in 60% propylene glycol with

40% sodium citrate and both solutions were injected *i.p.* (page 542, left column, "Materials and Methods"). Figure 1 (page 543) demonstrates that DMXAA and melphalan can be administered concomitantly or sequentially and in both cases DMXAA potentiates the effect of melphalan. The reference thus further suggests that DMXAA can enhance the antitumor effect of a chemotherapeutic agent, likely through its inhibition of tumor blood flow which results in the entrapment of the alkylating agent caused by falling tumor blood flow (page 545, right column, last full paragraph). The authors conclude that the study demonstrates the potential of DMXAA to "induce microenvironmental changes in tumors that can be exploited by bioreductive drugs and other agents with selectivity for hypoxic and/or acidic conditions (*id.*). The reference does not explicitly suggest combining DMXAA with gemcitabine.

However, van Moorsel *et al.* disclose combination chemotherapy studies with gemcitabine and etoposide in non-small cell lung and ovarian cancer cell lines. These antineoplastic agents are known in the art to have clinical activity against various solid tumors (Abstract). Because gemcitabine and etoposide have different mechanisms of action, the drugs were combined and studied *in vitro*. Gemcitabine has clinical activity in several solid tumors, such as ovarian cancer, NSCLC, head and neck cancer, and pancreatic cancer (page 407). Gemcitabine becomes phosphorylated to its triphosphate and is subsequently incorporated into DNA, followed by one or more deoxynucleotides after which DNA polymerization stops. Etoposide is a widely used anticancer agent that inhibits topoisomerase II (pages 407-408). Gemcitabine was solubilized in PBS for the experiments (page 408). The combined chemotherapy was shown to be synergistic in ovarian and NSCLC cells lines (Table 2). The reference thus suggests combining

gemcitabine with other anticancer agents in the treatment of cancer and further demonstrates that such a combination could be synergistic in nature.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to administer DMXAA in combination with gemcitabine as taught by Siemann *et al.* in view of Pruijn *et al.* and van Moorsel *et al.* One would have been motivated to do so because each of the therapeutics have been individually taught in the prior art to be successful at treating cancer, and further, Siemann *et al.* and Pruijn *et al.* explicitly teach combination therapy for the treatment of cancer using DMXAA and a second therapeutic agent. Moreover, the instant situation is amenable to the type of analysis set forth in *In re Kerkoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, one of ordinary skill in the art would have been imbued with at least a *reasonable expectation of success* that by administering DMXAA in combination with gemcitabine as taught in Siemann *et al.* in view of Pruijn *et al.* and van Moorsel *et al.*, one would achieve a method of treating cancer.

Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

Finally, it is clear from the prior art that DMXAA potentiates the antitumor effect of a number of anticancer agents (*e.g.* cisplatin, cyclophosphamide and melphalan) because of its mechanism of action (inhibiting tumor blood flow). One skilled in the art would have been imbued with at least a **reasonable expectation** that DMXAA would also potentiate the effect of the anticancer drug gemcitabine.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

U.S. Non-Provisional Application No. 11/592,678

Claims 1-4, 7-8, 11-13, 16-17 and 20-21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of copending Application No. 11/592,678. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '678 application recite methods, compositions, processes, and kits comprising DMXAA and other compounds, including the instantly claimed gemcitabine.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

June 5, 2007

Phyllis Spivack

PHYLLIS SPIVACK
PRIMARY EXAMINER